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### ► To cite this version:

Geneviève Giraldeau, Nicolas Duchateau, Bart Bijnens, Luigi Gabrielli, Diego Penela, et al.. Dyssynchronization reduces dynamic obstruction without affecting systolic function in patients with hypertrophic obstructive cardiomyopathy: a pilot study. *International Journal of Cardiovascular Imaging*, 2016, 32 (8), pp.1179-1188. 10.1007/s10554-016-0903-3 . hal-02282402

**HAL Id: hal-02282402**

**<https://hal.science/hal-02282402>**

Submitted on 11 Sep 2019

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# Dyssynchronization reduces dynamic obstruction without affecting systolic function in patients with hypertrophic obstructive cardiomyopathy: a pilot study.

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**Word count (excluding tables): 3075 words**

**Number of tables: 3**

**Number of figures: 4**

## **Acknowledgements / funding**

The authors acknowledge the Spanish Industrial and Technological Development Center (cvRemod-CEN-20091044), the Subprograma de Proyectos de Investigación en Salud, Instituto de Salud Carlos III, Spain (FIS-PI11/01709), the Plan Nacional I+D+I (DEP2010-20565), the Comisión Nacional de Ciencia y Tecnología (FONDAP-15130011), and the European Union 7th Framework Programme (VP2HF-FP7-2013-611823). GG was awarded the grant Bal Du Coeur from the Fondation de l'Institut de Cardiologie de Montréal.

**Disclosures / conflict of interest:** none declared.

## Abstract

*Purpose:* Dyssynchrony from biventricular pacing (BiV) can reduce dynamic obstruction in hypertrophic obstructive cardiomyopathy (HOCM), but its consequences on the left ventricular (LV) systolic function are unknown. We evaluate changes in LV systolic function and assess the effectiveness of BiV in HOCM.

*Methods:* 13 patients with HOCM (55[33/75] years, 5 males) received a BiV device and underwent 2D transthoracic echocardiography before the implantation and at 12 months follow-up. Global longitudinal and radial strain, and the timing of segmental displacement curves were measured by commercial speckle-tracking software to assess LV systolic function and dyssynchrony.

*Results:* Peak gradient in the LV outflow tract (LVOT) significantly decreased from 80[51/100] to 30[5/66] mmHg ( $p=0.005$ ). LV global strain was preserved from baseline to follow-up: 35.1[20.2/43.8]% vs. 32.6[27.1/44.1]%,  $p=NS$  (radial), and -16.6[-19.1/-14.4]% vs. -15.7[-17.0/-14.2]%,  $p=NS$  (longitudinal). Dyssynchrony analysis using displacement curves showed inversion of wall motion timing with earlier displacement of the lateral wall at follow-up only in patients with reduction in LVOT gradient.

*Conclusions:* BiV reduces LVOT obstruction in patients with HOCM when dyssynchronization of LV motion and inversion of the timing of LV wall activation are reached. Notably, this does not lead to further deterioration of LV systolic function at mid-term follow-up.

## Keywords

Speckle-tracking; Myocardial strain; Biventricular pacing; Hypertrophic obstructive cardiomyopathy.

## **Abbreviations**

**AV:** atrio-ventricular

**BiV:** Biventricular pacing

**HOCM:** Hypertrophic obstructive cardiomyopathy

**LV:** Left ventricle

**LVOT:** Left ventricle outflow tract

**RV:** Right ventricle

## Introduction

Sixty percent of patients with hypertrophic cardiomyopathy have significant ( $\geq 30$  mmHg) left ventricular outflow tract (LVOT) obstruction, either at rest or after provocation (e.g. a Valsalva maneuver), which contributes to symptoms and increases the risk of sudden cardiac death [1]. Dual-chamber pacing is an alternative to surgical therapy or alcohol septal ablation [1].

However, controversial results for dual-chamber pacing efficacy [2] led to the research of alternative modes of pacing. Moreover, recent long-term follow-up data has raised concerns about chronic dual-chamber pacing in HOCM patients and a possible deleterious effect on survival and heart failure [3]. In accordance with this finding, some studies suggested that right ventricular (RV) pacing deteriorates left ventricular function in patients with HOCM both acutely and on the long-term run [4-6]. Similarly, studies in the population with normal or reduced ventricular function and without hypertrophic cardiomyopathy have showed an association between RV-pacing and the deterioration of left ventricle (LV) ejection fraction and the augmentation of the risk of hospitalization for heart failure [7-12].

As an alternative, biventricular pacing (BiV) to reduce dynamic obstruction in hypertrophic obstructive cardiomyopathy (HOCM) has yielded encouraging results for reducing intraventricular obstruction and for clinical improvement [13-21]. However, while its effectiveness was demonstrated, the long-term effect of BiV-pacing on LV function among patients with HOCM and preserved LV ejection fraction is unknown.

The main contribution of this study consists in investigating the consequences of BiV on LV deformation, to determine whether the benefits of pacing-induced dyssynchrony are not hindered by lower LV systolic function. We previously reported on the effects of BiV in terms of LVOT pressure gradient and LV motion on 9 patients with HOCM [13]. The present study extends this work by a more comprehensive assessment of LV systolic function with deformation imaging at mid-term follow-up.

## Methods

### Patients

Between November 2005 and January 2013, 18 consecutive HOCM patients with significant LVOT obstruction (baseline intraventricular gradient  $\geq 50$  mmHg), LV ejection fraction  $\geq 50\%$ , sinus rhythm and severe symptoms despite optimum medical treatment and without indication for pacing due to bradycardia, were referred for BiV. Patients were accepted in the study only if surgical myomectomy or septal ablation were contraindicated (due to severe renal insufficiency, chronic obstructive pulmonary disease, liver cirrhosis) or were refused by the patient. Our institution's Ethics committee approved the study protocol, and written informed consent was obtained from all patients. Patients were defined as responders to BiV if they completed both of the following criteria for reduction of obstructive gradient: (i) follow-up gradient  $\leq 50$  mmHg and (ii) reduction in LVOT pressure gradient of at least 50% from baseline.

### Cardiac resynchronization therapy device implantation

The technique for device implantation has been described in detail elsewhere [13]. In brief, right leads were positioned conventionally in the right atrial appendage and RV apex. The LV lead was inserted via the coronary sinus and subsequently inserted in a ventricular vein and positioned as laterally as possible on the LV free-wall. All leads were connected to a dual-chamber biventricular implantable device and patients considered being at high risk for sudden cardiac death also received a cardioverter-defibrillator.

### Echocardiographic evaluation

All patients underwent standard transthoracic two-dimensional echocardiography before implantation, one day after implantation (for programming optimization) and follow-up. Parasternal and apical echocardiographic images were obtained with a commercially available system (Vivid7 and E9, GE Healthcare, Milwaukee, WI) using a 3.5-MHz transducer.

LV wall thickness and diameters were measured from the parasternal long-axis view using M-mode or 2D measurements at mitral valve leaflet tips level. LV mass was calculated using the Devereux

formula [22]. LV volumes and ejection fraction were obtained using the biplane Simpson method. The peak LVOT pressure gradient was determined using continuous wave Doppler from the apical five-chamber view and was measured under resting conditions and after a provocative Valsalva maneuver. Values were determined by averaging measurements obtained in three consecutive cardiac cycles.

Analysis of LV global radial and longitudinal strain was performed from the short-axis view at the papillary muscles level (average of 6 LV segments) and from 4-chamber apical (average of 6 LV segments) view, respectively, using commercial software (2D strain, Echopac, GE Healthcare). We have chosen to analyze GLS only in the 4-chamber as it allows visualizing the septum and the anterolateral wall in the same view, which is of interest to properly assess the changes induced by pacing. Besides, the reliable image quality of this view for strain quantification was also a criterion for privileging it while keeping measurements as simple as possible. The timing of displacement of opposing LV walls was assessed in the short-axis view at the papillary muscles level using displacement curves obtained by speckle-tracking. This view was chosen to explore the mechanisms gradient reduction as the dynamic obstruction predominates at this level. The sample of tissue interrogation was placed in the antero-septal and infero-lateral LV segments. In order to highlight the timing of wall motion, we measured the time-to-onset of radial displacement (from beginning of QRS to beginning of wall displacement) and time-to-peak of radial displacement (from beginning of QRS to peak systolic displacement). Comparison of timings between baseline and follow-up was made comparing infero-lateral to antero-septal (negative time value signifying that infero-lateral wall motion occurs first, and positive time value signifying that antero-septal displaces first).

#### **Optimization of the programming of the BiV device**

The algorithm for the optimization of the programming has been previously described elsewhere [13]. The optimum AV interval was considered as the shortest AV interval without A-wave truncation on the mitral inflow. Subsequently, ventricular pacing mode was selected testing RV-only pacing, LV-only pacing, or BiV-pacing with 4 different programs (RV preactivation VV+30ms, simultaneous BiV-pacing VV0ms, or LV preactivation VV-30ms, -60ms). The final pacing configuration was selected according to the maximum reduction of LVOT gradient after a 5 min equilibrium phase for each setup. The echocardiographer was blinded to pacing configuration.

### Statistical analysis

Due to the sample size of the study population, non-parametric test were used. Quantitative variables were expressed as median and first/third inter-quartile range while qualitative variables were described as number of cases (% from reference population). Paired dichotomous and quantitative variables were compared using Chi-square and Wilcoxon tests, respectively. A p-value <0.05 was considered statistically significant.

## Results

Of the 18 patients, 1 did not complete the mid-term follow-up at the moment of analysis, and 4 patients did not have images available for strain analysis, leaving a final cohort study of 13 patients with complete echocardiographic follow-up. Baseline characteristics are depicted in *Table 1*. Follow-up examination was performed at 12 months after implantation. Among the 13 patients in the study, optimum programming of the device based on maximum reduction in the LVOT gradient was VV+30 in 1 patient (8%), VV0 in 3 patients (23%), VV-30 in 7 patients (54%), VV-60 in 1 patient (8%) and LV (activation of LV only) in 1 patient (8%).

### LVOT Obstruction

Median peak LVOT gradient was 80[51/100] mmHg at baseline and significantly diminished [after the activation of the resynchronization device to 45\[20/60\] mmHg](#) and 30[5/66] mmHg at follow-up (p=0.005). Dynamic gradient with Valsalva maneuver was 110[78/130] mmHg before BiV and significantly diminished to 54[8/75] mmHg at follow-up (p=0.008).

According to the reduction of LVOT obstruction, 8 (62%) patients were classified as responders and 5 (38%) patients as non-responders to BiV. Individual behaviors are shown in *Figure 1*.

### Intra- and inter-observer variability

Repeatability in the extraction of myocardial motion, as conditioned by the speckle-tracking procedure, was previously reported [23]. These results are complemented by the measurements



summarized in *Figure 2*, which depict repeated curves along the whole cycle at basal septal/lateral levels and global values. Both indicate the low variability in the speckle-tracking measurements.

### **Impact of BiV on LV function**

There was no significant change in the LV function according to ejection fraction estimated by the Simpson method. LV ejection fraction was 71[67/73] % at baseline and 69[65/75] % at follow-up (p=NS). Similarly, the LV systolic function as assessed by strain analysis did not significantly changed at follow-up. Global LV radial strain was 35.1[20.2/43.8] % at baseline and 32.6[27.2/44.1] % at follow-up (p=NS). Global longitudinal LV strain was -16.6[-19.1/-14.4] % at baseline and -15.70[-17.0/-14.2] % at follow-up (p=NS). (*Table 2*) Segmental LV strain analysis (radial and longitudinal) was not significantly different between baseline and follow-up, with the exception of the longitudinal strain of the septal-apical segment (-23.8[-34.3/-22.6] % to -21.9[-24.4/-19.0] %, p=0.009). (*Figure 3*) Finally, reductions in septal and posterior wall thickness were observed without significant changes in LV cavity size after BiV. (*Table 1*) This trend was mainly observed in patients who reduced LVOT gradient (responders) as shown in *Table 2*.

### **Impact of BiV on LV dyssynchrony**

The changes in displacement of opposing LV walls from baseline to follow-up were significantly different between responders and non-responders to BiV (*Table 3*). In the responders, we observed a significant delay of the onset of antero-septal displacement (30[20/42] ms to 123[102/174] ms, p=0.028) combined with a non-significant delay of the onset of infero-lateral displacement (95[25/127] ms to 127[103/138] ms) with BiV resulting in a significant (p=0.046) inversion in the timing of wall motion as compared to baseline: onset changing from antero-septal first to infero-lateral first.

In the responders, we also observed a significant delay of the time to antero-septal peak displacement (363[320/407] ms to 542[481/577] ms) (p=0.028), combined with a non-significant delay of the time to infero-lateral peak displacement (421[358/515] ms to 418[367/455] ms) resulting in a significant (p=0.028) inversion in the timing of peak wall displacement as compared to baseline, changing from antero-septal wall first (infero-lateral 29[0/147] ms after antero-septal peak) to infero-lateral wall peak first (infero-lateral -108[-186/-62] ms before antero-septal peak).

The inversion of the timing of wall displacement (onset and peak) was absent in the non-responders. Representative examples of responder vs non-responder patients are illustrated in *Figure 4*.

## Discussion

In this study on patients with HOCM at mid-term follow-up, we demonstrate that (i) BiV does not affect LV systolic function, and that (ii) LVOT obstruction is reduced when dyssynchronization of LV motion and inversion of the timing of LV wall activation are reached. This reduction of dynamic obstruction is associated with a change in the timings of the motion of opposing LV walls.

### Biventricular pacing in HOCM

Current guidelines include cardiac pacing in HOCM as a class IIb indication and recommend dual-chamber pacing in patients without bradycardia indication who are symptomatic despite optimum medical treatment and who are suboptimal candidates for invasive septal reduction (surgical or alcohol reduction) [1]. Although, the initial results for dual-chamber pacing were positive, *Nishimura et al.* showed in a randomized trial a weak reduction of LVOT gradient (<50%) and no improvement in exercise capacity on a short-term follow-up, suggesting a placebo effect for the observed symptomatic improvement [2]. More recently, BiV has shown to induce a significant gradient reduction from  $74 \pm 23$  mmHg to  $28 \pm 17$  mmHg in 9 patients at 1-year follow-up in HOCM patients [13]. *Lenarczyk et al.* found similar results demonstrating significant reduction of peak gradient (60% reduction) in 9 patients with HOCM treated with BiV [15]. Similarly, smaller studies and case reports have shown the efficacy of BiV or LV-pacing for gradient reduction in the HOCM population [14,16-21]. Our results confirm a significant reduction of peak LVOT gradient at follow-up on a larger population (from  $80[51/100]$  mmHg to  $30[5/66]$  mmHg,  $p=0.005$ ).

### Dyssynchronization as mechanism for LVOT obstruction relief

The usual indication for BiV-pacing is for symptomatic patients with low LV ejection fraction ( $\leq 35\%$ ) with QRS prolongation and is aimed at resynchronizing electromechanical activity of the heart with

the goal of improving ventricular function [24]. It is important to emphasize that the objective of BiV-pacing in patients with HOCM is different, as it is indeed intended to dyssynchronize ventricular contraction and change the pattern of mechanical activation in order to reduce the dynamic obstruction. Using wall displacement traces (antero-septal and infero-lateral segments), we observed the inversion of the order of wall displacement, only in the responders, suggesting that the induced mechanical dyssynchrony plays a role in the reduction of LVOT obstruction.

### **Impact of BiV-pacing on LV function**

In our population, we found a global LV longitudinal strain of  $-16.6[-19.1/-14.4]\%$  and radial strain was  $35.1[20.2/43.8]\%$  at baseline, consistent with impaired LV myocardial deformation [25]. These findings are in keeping with previous reports describing reduced myocardial strain despite normal or supranormal LV ejection fraction in HOCM patients [26-28].

Additionally, as shown in previous studies [26-29], regional septal longitudinal deformation is markedly reduced and this does not change after BIV-pacing. To our knowledge, the long-term effect of BiV-pacing on LV function in HCOM is unknown and our data are the first to reveal non-significant changes in LV radial and longitudinal strain or in LV ejection fraction.

### **RV-pacing in HCOM**

From our results, the induced change in mechanical displacement of the LV free-wall, towards moving before the septum, is crucial for response. Therefore, the actual controversy about efficacy and placebo effect for RV-pacing in HOCM might be explained by the induction of a too small motion change of the interventricular septum, possibly due to the site of pacing being too close to the LV apex. By changing the timing of mechanical LV activation and inverting LV wall displacement, BiV might create changes in the 3-dimensional geometry of the LVOT and mitral valve apparatus resulting in the reduction of obstruction. As previously demonstrated [13], the acute reduction of gradient with BiV-pacing supports this mechanical explanation for response and is corroborated by other short-term studies [15-17,19-21,30]. On a long-term basis, LV reverse remodeling might play an additional role as shown by significant reduction of septal and posterior wall thickness. Previous studies showed that in HOCM patients treated with RV-pacing, there was a gradient reduction during follow-up even when pacing was

turned off, suggesting a role of remodeling on the longer term [31].

### **Impact of RV-pacing on LV function**

LV dysfunction as a consequence of chronic RV-pacing is becoming an increasingly recognized entity in patients without HCM. In the PACE trial, deterioration of ejection fraction in the RV-pacing group was observed in comparison to no change of ejection fraction in CRT-pacing group [7,8]. The MOST study showed that cumulative percentage of pacing was a predictor for heart failure hospitalization [9,10]. Similarly, *Tantengco et al.* showed significant LV deterioration at long-term follow-up in 24 patients with congenital AV block in comparison to controls [11]. The DAVID study also showed that RV-pacing might be deleterious and increase heart failure events in some patients with ejection fraction  $\leq 40\%$  [32].

In hypertrophic cardiomyopathy, results are controversial. *Lucon et al.* reported the very long-term follow-up of 51 patients with HOCM treated with dual-chamber pacing and showed a non-significant reduction of ejection fraction (64% to 56%) [4]. *Nishimura et al.* and *Betocchi et al.* found LV diastolic and systolic deterioration during acute RV-pacing [5,6]. Moreover, recent long-term follow-up data in HOCM patients showed possible deleterious effect on survival and heart failure of RV-pacing in comparison to other management [3]. Conversely, others have showed no EF deterioration with dual-chamber pacing [31,33].

While there is increasing evidence that RV-pacing deteriorates LV function in a lot of clinical settings, BiV-pacing has not been shown to induce the same effect and has rather been suggested as corrective therapy for RV-pacing induced LV dysfunction. This, together with our findings, suggests a benefit for preferring BiV-pacing in the HOCM population.

### **Limitations**

The main limitation of this study is the small cohort of patients. Low study size might hinder the power of statistical comparisons and in particular the assessment of the lack of differences. Thus, our findings are preliminary data and have to be confirmed by larger studies. Nonetheless, it has to be noted that experience with BiV in HOCM patients is worldwide limited, and that our study presents a broader

population than previously published works.

We are aware that choosing a definition for response to classify responders and non-responders is arbitrary but the criteria were chosen taking into consideration what might appear to be clinically relevant. A spectrum of response would be preferable but this was impossible considering the population size.

We are also aware about the limitations of dyssynchrony measures especially when considered as predictors of outcome; however, it was not our principal objective, but rather an exploratory research for the mechanism of action. Moreover, inherent characteristics of HOCM (myocardial fiber disarray, markedly abnormal strain [34,35] and heterogeneous involvement of LV myocardial segment) pose a challenge for motion analysis. Potentially, more precise methods for the quantification of motion changes between baseline and follow-up may allow depicting more comprehensively these changes [23]. Besides, our analysis was only performed at rest. Its extension to stress conditions may be of added value, and should be considered for future studies.

## Conclusions

Our results show that BiV reduces LVOT obstruction in patients with HOCM, by dyssynchronizing LV motion and inverting the timing of LV wall activation. Our study confirms that BiV-pacing is efficient in this task, as this does not lead to further deterioration of LV systolic function at mid-term follow-up. This is clinically reassuring and suggests a benefit for preferring BiV-pacing in the HOCM population. The confirmation of this finding would deserve further prospective larger studies.

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**Table 1. Baseline and follow-up characteristics of the studied population (N=13).** Data are expressed as median (1st/3rd quartiles).

	Baseline	Follow-up	p-value
Sex (female,%)	8 (62%)		NS
Age (years)	55 (33/75)		NS
Rest LVOT gradient (mmHg)	80 (51/100)	30 (5/66)	0.005
Provoked LVOT gradient (mmHg)	110 (78/130)	54 (8/75)	0.008
NYHA class (patients,%)			
I - II	3 (23)	10 (77)	p<0.005
III-IV	10 (77)	3 (23)	p<0.005
Heart Rate (bpm)	67 (58/74)	62 (55/71)	NS
QRS duration (ms)	85 (79/102)	120 (113/125)	0.011
E/A ratio	1.6 (0.9/1.9)	1.3 (0.6/1.5)	p<0.005
LVEDV (ml)	44 (35/49)	39 (35/49)	NS
LVESV (ml)	12 (10/17)	12 (9/16)	NS
LVEF (%)	71 (67/73)	69 (65/75)	NS
Short-axis radial strain (%)	35.1 (20.2/43.8)	32.6 (27.1/44.1)	NS
4-chamber longitudinal strain (%)	-16.6 (-19.1/-14.4)	-15.7 (-17.0/-14.2)	NS
Septal thickness (mm)	20 (18/27)	20 (16/26)	0.028
Posterior wall thickness (mm)	12 (11/13)	11 (10/12)	0.016
LV mass (g)	247 (203/363)	257 (171/364)	NS

LVEDV = Left ventricular end-diastolic volume, LVESV = Left ventricular end-systolic volume, LVOT = Left ventricular outflow tract.

**Table 2: LV remodeling and systolic function with BiV in responders and non-responders.** Data are expressed as median (1st/3rd quartiles).

	Responders (n=8)		Non-Responders (n=5)	
	Baseline	Follow-up	Baseline	Follow-up
<b>Rest LVOT gradient (mmHg)</b>	96 (40/111)	15 (0/30)*	76 (64/83)	70 (55/88)
<b>Provoked LVOT gradient (mmHg)</b>	111 (71/149)	33 (0/56)*	110 (85/120)	76 (72/120)
<b>Heart rate (bpm)</b>	60 (56/72)	60 (52/71)	68 (63/82)	67 (59/74)
<b>LVEDV (ml)</b>	45 (39/54)	40 (34/60)	44 (35/49)	39 (35/49)
<b>LVESV (ml)</b>	12 (10/18)	13 (11/16)	12 (10/17)	12 (9/16)
<b>LVEF (%)</b>	71 (67/74)	69 (65/75)	69 (63/72)	71 (55/74)
<b>LV radial strain (%)</b>	31.4 (22.9/48.1)	32.1 (25.4/40.2)	37.3 (14.5/43.5)	35.5 (23.8/55.9)
<b>LV longitudinal strain (%)</b>	-17.1 (-20.0/-14.7)	-15.6 (-17.1/-14.7)	-14.7 (-17.8/-12.5)	-13.8 (-17.4/-11.7)
<b>Septal thickness (mm)</b>	24 (19/28)	21 (18/26)	19 (17/27)	16 (15/26)
<b>LV Posterior wall thickness (mm)</b>	12 (10/13)	11 (10/11)†	12 (12/14)	12 (11/14)
<b>LV mass (g)</b>	358 (215/364)	268 (203/378)	239 (187/374)	227 (136/379)

LVOT = Left ventricle outflow tract, LVEDV = Left ventricular end-diastolic volume, LVESV = Left ventricular end-systolic volume, LVEF = Left ventricular ejection fraction; \* p<0.02 (baseline vs. follow-up); † p<0.05 (baseline vs. follow-up).

**Table 3: Analysis of mechanical LV dyssynchrony with LV radial displacement in responders and non-responders to BiV.**

		Responders (n=8)		Non-Responders (n=5)	
		Baseline	Follow-up	Baseline	Follow-up
Time-to-onset of wall displacement (ms)	$\Delta$ Time-to-onset (IL-AS)	74 (-4/86)	-16† (-60/31)	0 (0/15)	-19 (-71/-6)
	Septal Onset (ms)	30 (20/42)	123* (102/174)	30 (21/52)	90† (58/118)
	Infero-Lateral Onset (ms)	95 (25/127)	127 (103/138)	30 (21/67)	45 (28/84)
Time-to-Peak wall displacement (ms)	$\Delta$ Time-to-peak (IL-AS)	29 (0/147)	-108* (-186/-62)	0 (-8/137)	0 (-177/37)
	Septal peak (ms)	363 (320/407)	542* (481/577)	363 (285/374)	441 (385/488)
	Infero-Lateral peak (ms)	421 (358/515)	418 (367/455)	368 (364/422)	374 (287/479)

AS: Anteroseptal, IL: infero-lateral; \* p<0.03 (baseline vs. follow-up); † p<0.05 (baseline vs. follow-up).

## Figures legend

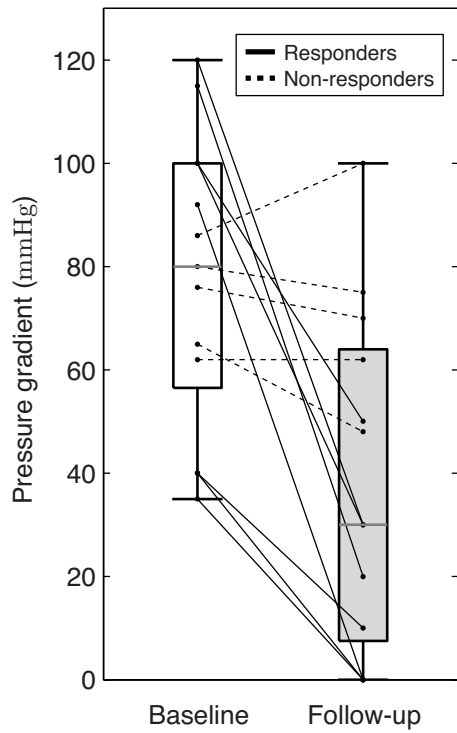
### Figure 1: LVOT pressure gradient evolution

**Figure 2: Repeatability in the extraction of radial displacement and global longitudinal strain**, as conditioned by the speckle-tracking procedure. Traces shown for the basal septal and lateral wall locations (radial displacement, left) and the whole myocardium (global longitudinal strain, right). *Left*: Intra-observer variability (single observer, single cycle, repeated 10 times). *Middle*: Inter-observer variability (2 different observers, single cycle). *Right*: Influence of the echocardiographic data (single observer, 3 consecutive cycles and 1 additional cycle from another sequence of the same patient [4-chamber view zoomed-in on the LV])

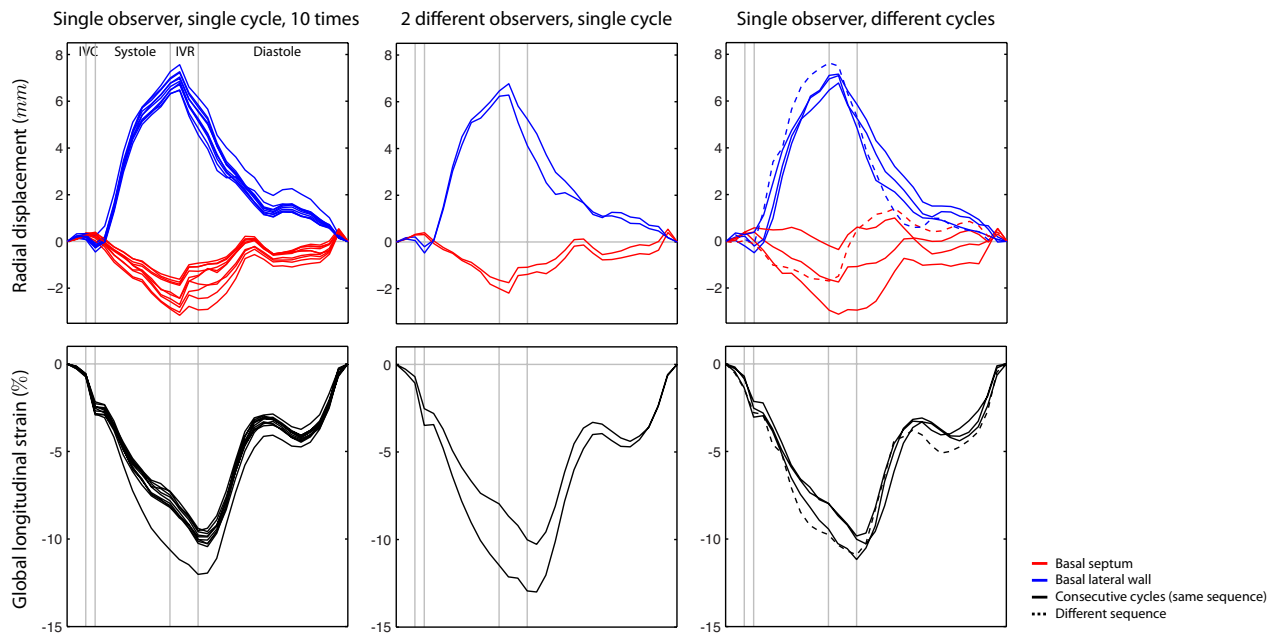
**Figure 3: Global and segmental strain analysis: Baseline to Follow-up.** *Left*: segmental and global radial peak systolic LV strain derived from the short-axis view at baseline (white) and follow-up (black). *Right*: segmental and global longitudinal peak systolic LV strain derived from the 4-chamber view at baseline (white) and follow-up (black). All non-significative changes from baseline to follow-up with exception of AS segment; \* $p=0.009$ ; AS=Antero-septal, IS=Infero-septal, I=Inferior, IL=Infero-lateral, AL=Antero-lateral, A=Anterior. BS=Basal-septal, MS=Medio-Septal, ApS=Apical-septal, ApL=Apical-lateral, ML=Medio-lateral, BL=Basal-lateral.

**Figure 4: Short-axis displacement curves:** Specific behavior of a responder (top) versus a non-responder (bottom) patient from baseline (left) to follow-up (right) *Top*: Typical pattern of displacement from baseline to follow-up in a responder. (yellow curve: antero-septal, blue curve: infero-lateral). Observe the inversion and delay of septal onset of displacement (yellow arrow) and the inversion of peak displacement at follow-up. *Bottom*: Typical pattern of displacement from baseline to follow-up in a non-responder. (yellow curve: antero-septal, blue curve: infero-lateral). Observe the absence of temporal inversion and delay of antero-septal onset of displacement (yellow arrow) and the absence of peak displacement inversion at follow-up.

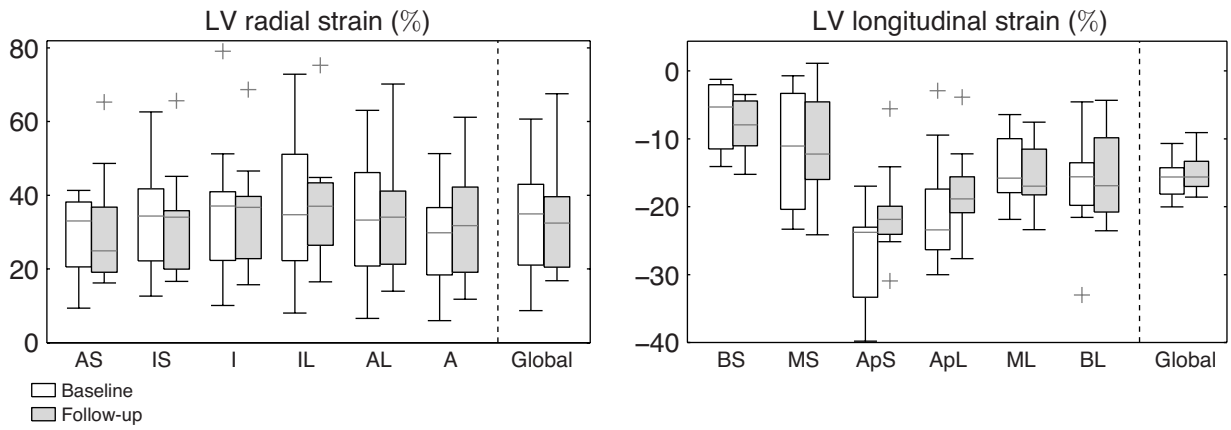
**Figure 1**



**Figure 2**



**Figure 3**



**Figure 4**

